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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,448	06/26/2000	Susan Margaret Thomas	M&G 10552.26-US-01	3487

23552 7590 11/22/2002

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/22/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/603,448	Thomas
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 11-16, 19-24, 56, and 58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 11-16, 19-24, 56, and 58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e) was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 18, 2002 has been entered.

Claim Objections

2. Claims 8, 23 and 58 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Specifically, claims 8, 23 and 58 all relate to performing the method of contacting cells which are in logarithmic phase, while claim 1 and claim 56 are limited to contacting cells which are in stationary phase. Logarithmic growth is not a subset or element of stationary phase. Logarithmic phase and stationary phase are entirely different elements which do not encompass one another. Thus, claims 8, 23 and 58 broaden the independent claim from which they depend and are improper.

Claim Rejections - 35 USC § 112

3. Claims 1-8, 11-27, 56 and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are indefinite because it is unclear whether the limitation in independent claim 1 and claim 56 to "host cell being in stationary growth phase" is, in fact, truly a limitation of the claims. The presence of three claims, 8, 23 and 58, which depend from claims and 56 and which permit logarithmic growth make the metes and bounds of the claim indefinite. If the claims are read to actually limit the host cell to stationary growth phase, the prior art rejections below are not applicable. However, if the claims metes and bounds permits the cells to be in logarithmic growth phase as is indicated, for example, by new claim 58, then the rejections below are proper. Therefore, because the presence of claims 8, 23 and 58 renders the metes and bounds of the independent claims vague and indefinite, the prior art rejections below are maintained. Amendment to cancel claims 8, 23 and 58 and clearly indicate that the method involves only host cells in the stationary phase would overcome this rejection and the prior art rejections below.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-8, 11-14, 16 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Justus et al (Mutation Research (1998) 398:131-141) in view of Chalfie et al (Science (1994) 263:802-804)

Justus teaches a method of determining a mutagen comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably linked to a mutagen sensitive gene such as umuC which is an SOS gene (page 133, column 1), b) monitoring a host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth and incubating the host cells at 37C with shaking (page 134, column 1), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into phosphate buffer (page 134, column 1), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (page 134, column 2). Justus further teaches detection using a range of concentrations of the test compound (page 137, figure 6). Justus teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on page (page 137, figure 6 and page 134, column 2).

Justus does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Justus using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase reporter protein used by Justus since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

6. Claims 1-8, 11-16, 21-24 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804).

Farr teaches a method of determining a mutagen (column 5, ines 8-15) comprising: a) contacting a test compound with a host cell comprising a DNA sequence encoding a reporter protein operably linked to a mutagen sensitive gene (column 19, line 40 to column 20, line 19 and column 29, example 7) such as dinD which is an SOS gene (column 7, lines 3-15), b) monitoring a

host cell preparation for reporter protein by diluting the host cells which are in logarithmic growth or stationary growth and incubating the host cells at 37C with shaking (column 14, lines 5-65), where the dilution solution may starve the host cell by depleting a nutrient such as dilution into minimal media (Column 14, lines 10-12), c) determining a mutagen when an amount of reporter protein meets or exceeds a predetermined threshold value (columns 29-31, example 7). Farr further teaches detection using a range of concentrations of the test compound (column 30, table 1). Farr teaches using analyzing a change in the shape of the data comparing a control cell with the test compound as shown on (figure 9-12). Farr further teaches identification methods to detect antimutagens (column 31, example 8). Farr expressly teaches screening in 96 well microtiter plates (column 31, line 27).

Farr does not teach the use of green fluorescent protein as the reporter gene, nor the specific wavelengths of excitation and detection.

Chalfie teaches the use of the green fluorescent protein as a reporter gene and teaches that the protein is excited at 485 nm and detected at 509 nm (page 802, column 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr using a luciferase reporter gene and replace the luciferase reporter gene with the GFP protein of Chalfie since Chalfie states "Several methods are available to monitor gene activity and protein distribution within cells. These include the formation of fusion proteins with coding sequences for b-galactosidase, firefly luciferase and bacterial luciferase. Because such methods require exogenously added substrates

or cofactors, they are of limited use with living tissue. Because the detection of intracellular GFP requires only irradiation by near UV or blue light, it is not limited by the availability of substrates. Thus it should provide an excellent means for monitoring gene expression and protein localization in living cells (page 803, column 3)". An ordinary practitioner would have been motivated to substitute the GFP protein of Chalfie for the luciferase or galactosidase reporter protein used by Farr since Chalfie notes that the GFP protein does not require exogenous cofactors, is no limited by substrate availability and can be easily detected by irradiation with UV or blue light.

7. Claims 1-8, 11-16, 19-24, 56 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Farr (U.S. Patent 5,589,337) in view of Chalfie et al (Science (1994) 263:802-804) and further in view of Mitchell et al (Mutation Research (1986) 159:139-146).

Farr in view of Chalfie teach the limitations of claims 1-8, 11-16, 21-24 and 56 as discussed above. Farr in view of Chalfie do not teach the use of the Kolmogorov Smirnov test with selection of a P value less than .05.

Mitchell teaches the use of a Kolmogorov Smirnov test for the analysis of data regarding the ability of mutagens to effect a reporter system and show a number of Significance levels including $P<.05$ (page 142, table 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the detection method of Farr in view of Chalfie with the use of the Kolmogorov Smirnov statistical test of Mitchell since Mitchell states "It was concluded that the non-parametric Kolmogorov-Smirnov two-sample test was the most reliable method of

analysis (abstract)". An ordinary practitioner would have been motivated to use the Kolmogorov-Smirnov test because it was a normal statistical analysis tool which was identified as the most reliable in determining which mutagens were statistically significant.

Response to Arguments

8. Applicant's arguments filed October 18, 2002 have been fully considered but they are not persuasive.

Applicant argues that the newly amended claims 1 and 56 distinguish over the 35 U.S.C. 103 rejections because the limitation of contacting the cells in the stationary phase is present in these claims. As noted above, the presence of dependent claims in which the contacting occurs in logarithmic phase renders the scope and the metes and bounds of the independent claims uncertain and indefinite. Based upon this indefiniteness, the prior art rejections are maintained. Due to the new grounds of rejection, in particular the new 112, second paragraph rejection, this action is nonfinal.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

November 20, 2002